UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,012	04/03/2001	Robert Young	43191-256808 (J&A16210-25	3957

23594 7590 10/31/2003

JOHN S. PRATT
KILPATRICK STOCKTON LLP
1100 PEACHTREE
SUITE 2800
ATLANTA, GA 30309

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	16

DATE MAILED: 10/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,012	YOUNG, ROBERT	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *23-28 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8 and 13* is/are rejected.

7)☐ Claim(s) *9-12,14-22, 29-31 and 33-36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Acknowledgement is made of applicants election without traverse of Group I, drawn to compounds comprising a target cell specific portion and a cytotoxic portion, said cytotoxic portion having endonucleolytic activity, pharmaceutical compositions thereof and methods for preparing medicaments comprising said compounds.

2. Claims 1-36 are pending. Claims 23-28 and 32, drawn to non-elected inventions, are withdrawn from consideration. Claims 1-22, 29-31 and 33-36 are under consideration. Claims 33-36 will be examined to the extent that they depend on claim 31

Priority

3. Acknowledgement is made of applicant's claim to priority of GB 0008049.9, filed April 3, 2002. However, neither a copy of said application or the patent issued therefrom could not be located in the file or in the foreign patent databases. Accordingly, priority is granted only to 60/237, 159.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It claims priority to application GB 0008049.9 which cannot be located on the foreign patent databases. Submission of the priority application could overcome this objection.

Claim Objections

5. Claims 9-12, 14-22, 29-31 and 33-36 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim. Multiple dependent claims, such as claim 4, cannot serve as the basis for other multiple dependent claims. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits. It is also noted that claims

16 and 19 do not conform to the Sequence Rules and Regulations, therefore Sequence identifiers are required for claim 16 and the "GSGG" peptide of claim 19.

6. Claims 1-3 are objected to because of the following informalities: The claims recite "an humanized HMFG-1 antibody" rather than "a humanized HMFG-1 antibody". Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7 and 8 refer to amino acid sequences encoded by nucleotide sequences of figure 3. Section 2173.05(s) of the MPEP states

> Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted). Reference characters corresponding to elements recited in the detailed description and the drawings may be used in conjunction with the recitation of the same element or group of elements in the claims. See MPEP § 608.01(m)

Thus, the claims are rendered vague and indefinite in that they are not complete in themselves as a result of relying on Figures within the specification. Amendment of the claims to recite the SEQ ID NO of the nucleotide or amino acid sequences would overcome this rejection.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 1-3, 7 and 8 are rejected under 35 U.S.C. 102(a) as being anticipated by Young et al (Proceed Amer Assoc Cancer Res, March 2000, Vol..41, page 289, reference of the IDS filed January 23, 2003).

Claim 1 is drawn to a compound comprising a target sell-specific portion and a cytotoxic potion characterized in that the target cell-specific portion comprises a humanized monoclonal antibody having specificity for PEM or an antigen binding fragment thereof and the cytotoxic portion has endonucleolytic activity. Claim 2 embodies the compound of claim 1 wherein the target cell specific portion comprises a humanized HMFG-1 antibody or an antigen binding fragment thereof. Claim 3 embodies the compound of claim 2 wherein the target cell specific portion is a humanized antibody. Claim 7 embodies the compound of claim 1 wherein the target cell specific portion comprises an amino acid sequence encoded by at least part of one or both of the nucleotide sequences of Figure 3(a) and (d). Claim 8 embodies the compound of claim 1 wherein the target cell specific portion comprises an amino acid sequence encoded by the nucleotide sequence of Figure 3(a) and an amino acid sequence encoded by the nucleotide sequence of Figure 3(d).

Young et al teach an immunotoxin comprising humanized HMFG1 and DNase I. The specification teaches that the amino acid sequences of Figures 3(a) and (d) are SEQ ID NO:7 and SEQ ID NO:10. The sequence listing identifies SEQ ID NO:7 as "humanized HMFG-1 light chain" and SEQ ID NO:10 as "humanized HMFG-1 heavy chain". Thus, a humanized version of HMFG-1 would comprise SEQ ID NO:7 and 10.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epenetos et al (WO 94/15644, reference of the IDS filed January 23, 2003) in view of Schlom

(In: Molecular Foundations of Oncology, 1991, pp. 95-134), Van Hoft et al (Cancer Research, 1996, Vol. 56, pp. 5179-5185) and Verhoyen et al (WO 92/04380, reference of the IDS filed January 23, 2003).

The specific embodiments of claims 1-3, 7 and 8 are recited above. Claim 4 comprises the compound of claim 1 or 2 wherein the target cell specific portion comprises an antigen binding fragment of the humanized antibody selected from the group consisting of Fab-like molecules, Fv molecules disulphide linked Fv molecules scFv molecules and single domain antibodies. Claim 5 embodies the compound of claim 4 wherein the target cell specific portion comprises a Fab molecule. Claim 6 embodies the compound of claim 4 wherein the target cell specific portion comprises a F(ab')2 molecule. Claim 13 embodies the compound of claim 1 wherein the endonuclease is a restriction endonuclease.

Epenetos et al teach a compound comprising a target cell specific portion and a cytotoxic portion characterized in that the cytotoxic portion has DNA endonucleolytic activity (page 3, lines 12-17), and specifically that the DNA endonuclease could be a type II restriction endonuclease (page 27, lines 8-11). Epenetos et al teach the incorporation into the compound a nuclear targeting sequence (page 28, lines 23-26). Epenetos et al teach that the entity which is recognized by the target cell specific portion is an entity which is expressed by tumor cells and will often be recognized as an antigen, examples of which are set forth in Table 1 (page 6, lines 1-7). Table 1 includes PEM (page 10) recognized by the antibody HMFG1 antibody. Epenetos et al teach that the antibody could be a Fab-like molecule, Fv molecules, scFv and single domain antibodies (page 7, lines 1-10) or a humanized antibody (page 6, lines 20-23). Epenetos et al teach the fusion of a target cell specific portion with a cytotoxic portion by means of a synthetic linker (page 41, lines 10-13). Epenetos et al teach that a reagent which hydrolyses DNA would be particularly advantageous to rapidly dividing cells, such as tumor cells because during mitosis the nuclear membrane is dissolved and the cellular DNA is exposed (page 28, lines 16-21). Epenetos et al do not specifically teach the a compound comprising the HMFG1 antibody and a DNA endonuclease.

Schlom teaches that an immunotoxin is effective when internalized (page 107, second column, lines 5-10, under the heading "Drug and Toxin Conjugates"). Schlom teaches that it is unrealistic to assume that just one or tow administrations of a anti-cancer therapeutic would be

effective. Schlom points out that because of anti-HAMA responses against murine antibodies, only the first dose, and perhaps the second dose reached the tumor target. Schlom teaches that a solution to this problem is a humanized antibody (page 98, second column, line 29 to page 99, first column, line 4).

Van Hoft et al teach that the product of the MUC-1 gene, termed PEM, is internalized continuously, and therefore is a suitable antigen for antibody-directed therapy (page 5179, second column, first full paragraph).

Verhoyen et al teach humanization of the HMFG1 antibody (for example, page 21, line 19 to page 22, line 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to fuse the humanized HMGF1 antibody or an PEM-binding fragment thereof to a DNA endonuclease with endonucleolytic activity for treatment of tumors expressing PEM. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Epenetos et al regarding PEM as a target antigen and HMFG1 as the antibody which specifically binds to PEM; the teachings of Van Hoft regarding the internalization of PEM, and the teachings of Schlom regarding the effectiveness of immunotoxins which are internalized; the teachings of Schlom regarding the HAMA response to murine antibodies resulting in loss of delivered anti-tumor agent which is circumvented by the use of humanized antibodies and the teaching of Verhoyen et al on the humanization of HMFG1. One of skill in the art would be motivated to use humanized HMFG1 or a PEM binding fragment thereof in a fusion protein with a DNA endonuclease in order to delver the DNA endonuclease to tumor cells expressing the PEM antigen and undergoing rapid mitosis, because on of skill in the art would know that the binding of an antibody to the PEM antigen will result in the translocation of the antibody to the cytoplasm of the cell; one of skill in the art would also know that tumor cells are be more susceptible to a DNA endonuclease that cells not undergoing rapid mitosis because of the teachings of Epenetos et al regarding the nuclear membrane.

13. Claims 1-7 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epenetos et al (WO 94/15644, reference of the IDS filed January 23, 2003) in view of Pietersz et al (Cancer Immunol Immunother, 1997, Vol. 44, pp. 323-328). The specific embodiments of the

claims are set forth above. It is noted that when given the broadest reasonable interpretation, the recitation of "a portion" in claim 7 reads on a single amino acid. Therefore claim 7 embodies antibodies which have only one amino acid in common with HMFG1.

Epenetos et al teach a compound comprising a target cell specific portion and a cytotoxic portion characterized in that the cytotoxic portion has DNA endonucleolytic activity (page 3, lines 12-17), and specifically that the DNA endonuclease could be a type II restriction endonuclease (page 27, lines 8-11). Epenetos et al teach the incorporation into the compound a nuclear targeting sequence (page 28, lines 23-26). Epenetos et al teach that the entity which is recognized by the target cell specific portion is an entity which is expressed by tumor cells and will often be recognized as an antigen, examples of which are set forth in Table 1 (page 6, lines 1-7). Table 1 includes PEM (page 10) Epenetos et al teach that the antibodies can be used as target cell specific binding agents and said antibodies could be a Fab-like molecule, Fv molecules, scFv and single domain antibodies (page 7, lines 1-10) or a humanized antibody (page 6, lines 20-23). Epenetos et al teach the fusion of a target cell specific portion with a cytotoxic portion by means of a synthetic linker (page 41, lines 10-13). Epenetos et al teach that a reagent which hydrolyses DNA would be particularly advantageous to rapidly dividing cells, such as tumor cells because during mitosis the nuclear membrane is dissolved and the cellular DNA is exposed (page 28, lines 16-21). Epenetos et al do not specifically teach the a compound comprising an antibody which binds to the PEM antigen and a DNA endonuclease.

Pietersz et al teach the humanized CTMO1 antibody and the BC2 antibody binds to the MUC1 antigen (abstract, lines 1-4). The art teaches that MUC-1 is synonymous with PEM (see van Hoft, ibid, first column, lines 8-9). Pietersz et al teach that the most important property of an anti-MUC1 antibody for therapy is that said antibody should be rapidly internalized and have a rapid rate of association at 37 degrees (pages 323-324, bridging sentence). Pietersz et al teach that the affinity of the two antibodies for MUC-1 was essentially the same at 37 degrees but that radio labeled hCTMO1 antibody had a high rate of internalization compared to the radio labeled BC2 antibody (page 325, second column, lines 6-10 and Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to fuse the hCTMO-1 antibody or an PEM-binding fragment

thereof to a DNA endonuclease with endonucleolytic activity for treatment of tumors expressing PEM.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Epenetos et al regarding PEM as a target antigen and; the teachings of Pietersz et al regarding the necessity of internalization of the antibody which binds to MUIC-1 and the high internalization of the humanized CTMO1. One of skill in the art would be motivated to use hCTMO1 or a PEM binding fragment thereof in a fusion protein with a DNA endonuclease in order to delver the DNA endonuclease to tumor cells expressing the PEM antigen and undergoing rapid mitosis, because on of skill in the art would know that the binding of an antibody to the PEM antigen will result in the translocation of the antibody to the cytoplasm of the cell; one of skill in the art would also know that tumor cells are be more susceptible to a DNA endonuclease that cells not undergoing rapid mitosis because of the teachings of Epenetos et al regarding the nuclear membrane.

Conclusion

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Maraveyas et al (Cancer Research, 1995, Vol. 55, pp. 1060-1069); Monaco et al Annals of the New York Academy of Sciences, 1986, vol. 464, pp. 389-399)..

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
10/22/03

Karen A. Canella